STIC-ILL

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From: Holleran, Anne
Sent: Thursday, October 18, 2001 7:28 PM
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Subject: refs. for 09/512,363

Examiner: Anne Holleran
Art Unit: 1642; Rm 8E03
Phone: 308-8892
Date needed by: ASAP

Please send me copies of the following :

1. Wajant, J. et al. Cellular Signalling (2001) 13(6): 389-400
2. Baud, V. et al. Trends in Cell Biology (2001) 11(9): 372-377
3. Heynick, K. et al. Molecular Cell Biology Res. Communications (2001) 4(5): 259-265
4. Handel, M.L. et al. Clinical and Experimental Pharmacology and Physiology (2000) 27(3): 139-144
5. Jue, D.-M. et al. J. Korean Med. Sci. (1999) 14(3): 231-238

Article title	The TNF-receptor-associated factor family - Scaffold molecules for cytokine receptors, kinases and their regulators
Article identifier	089865680100050X
Authors	Wajant_H Henkler_F Scheurich_P
Journal title	Cellular Signalling
ISSN	0898-6568
Publisher	Elsevier USA
Year of publication	2001
Volume	13
Issue	6
Supplement	0
Page range	389-400
Number of pages	12
User name	Adonis
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PCC	$20.00
Date and time	Friday, October 19, 2001 9:39:47 PM

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=> d his

     (FILE 'HOME' ENTERED AT 19:13:28 ON 18 OCT 2001)

     FILE 'MEDLINE, EMBASE, BIOSIS, CAPLUS' ENTERED AT 19:13:37 ON 18 OCT 2001
L1         10499 S NF-KAPPAB
L2        316202 S CYTOKINE OR TNF OR ENDOKINE
L3          3630 S L1 AND L2
L4             8 S ENDOKINE
L5             2 S L4 AND L1
L6             1 DUP REM L5 (1 DUPLICATE REMOVED)
L7        141838 S TNF
L8          2579 S L7 AND L1
L9       2435309 S ACTIVAT?
L10         2258 S L9 AND L8
L11      2794473 S REVIEW
L12           27 S L10 AND L11
L13           19 DUP REM L12 (8 DUPLICATES REMOVED)
L14            0 S L13 AND L4
L15           27 S L13 OR L4
L16           23 DUP REM L15 (4 DUPLICATES REMOVED)
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	L #	Hits	Search Text
1	L7	1	endokine
2	L8	0	tnf adj ligand adj "6"

ENTRY DATE: Entered STN: 20010730
Last Updated on STN: 20010730
Entered Medline: 20010726

AB The ***TNF*** -receptor-associated factor (TRAF) family is a phylogenetically conserved group of scaffold proteins that link receptors of the IL-1R/Toll and ***TNF*** receptor family to signalling cascades, leading to the ***activation*** of ***NF*** - ***kappaB*** and mitogen- ***activated*** protein kinases. Furthermore, TRAF proteins serve as a docking platform for a variety of regulators of these signalling pathways and are themselves often regulated at the transcriptional and posttranslational level. In this ***review*** , we address the structural and molecular basis of TRAF protein functions and highlight their role in cytokine signalling.

L16 ANSWER 3 OF 23 MEDLINE
ACCESSION NUMBER: 2001469959 IN-PROCESS
DOCUMENT NUMBER: 21406283 PubMed ID: 11514191
TITLE: Signal transduction by tumor necrosis factor and its relatives.
AUTHOR: Baud V; Karin M
CORPORATE SOURCE: Laboratoire Oncogenese, Differenciation et Transduction du Signal, CNRS UPR9079, Institut Andre Lwoff, 7 rue Guy Moquet, 94801, Villejuif, France.
SOURCE: TRENDS IN CELL BIOLOGY, (2001 Sep) 11 (9) 372-7.
Journal code: C5K; 9200566. ISSN: 0962-8924.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20010830
Last Updated on STN: 20010830

AB Tumor necrosis factor alpha (TNFalpha) is a potent proinflammatory cytokine that plays an important role in immunity and inflammation, and in the control of cell proliferation, differentiation and apoptosis. TNFalpha is also the founding member of a still growing family of cytokines with diverse bioregulatory functions. Considerable progress has been made in understanding the molecular mechanisms that mediate TNFalpha-induced cellular responses. Binding of TNFalpha to its two receptors, TNFR1 and TNFR2, results in recruitment of signal transducers that ***activate*** at least three distinct effectors. Through complex signaling cascades and networks, these effectors lead to the ***activation*** of caspases and two transcription factors, AP-1 and ***NF*** - ***kappaB*** . Similar signaling mechanisms are likely to be used by other members of the ***TNF*** family. This ***review*** focuses on proteins that transduce the signals generated at ***TNF*** receptors to nuclear targets such as AP-1 and ***NF*** - ***kappaB*** .

L16 ANSWER 4 OF 23 MEDLINE
ACCESSION NUMBER: 2001345749 MEDLINE
DOCUMENT NUMBER: 21301916 PubMed ID: 11408795
TITLE: The role of Epstein-Barr virus in neoplastic transformation.
AUTHOR: Knecht H; Berger C; Rothenberger S; Odermatt B F; Brousset P
CORPORATE SOURCE: Institute for Clinical Research, Swiss Paraplegic Centre, Nottwil, Switzerland.. hans.knecht@paranet.ch
SOURCE: ONCOLOGY, (2001) 60 (4) 289-302. Ref: 148
Journal code: OHW; 0135054. ISSN: 0030-2414.
PUB. COUNTRY: Switzerland

09512363
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010730
Last Updated on STN: 20010730
Entered Medline: 20010726

AB In this ***review*** , we focus on new data from basic, translational and clinical research relating to the Epstein-Barr virus (EBV). Beside its well-known tropism for B lymphocytes and epithelial cells, EBV also infects T lymphocytes, monocytes and granulocytes. After primary infection, EBV persists throughout the life span in resting memory B cells, from where it is reactivated upon breakdown of cellular immunity. In the process of neoplastic transformation, the EBV-encoded latent membrane protein 1 (LMP1) oncogene represents the major driving force. LMP1 acts like a constitutively ***activated*** receptor of the tumor necrosis factor receptor family and allows the amplification or bypassing of physiological regulatory signals through direct and indirect interactions with proteins of the tumor necrosis factor receptor-associated factor (TRAF) family. TRAF2-mediated ***NF*** - ***kappaB*** ***activation*** , AP-1 induction and JAK3/STAT ***activation*** may result in sustained proliferation leading to lymphoma. The ability of LMP1 to suppress germinal center formation and its capacity to mediate its own transcriptional ***activation*** shed new light on the pathogenesis of EBV-associated latency type II lymphoproliferations like Hodgkin's disease and angioimmunoblastic lymphadenopathy. The carboxy terminus of LMP1 is also a reliable marker for individual EBV strain identification and thus offers new possibilities in tracing the molecular events leading to posttransplant lymphoproliferative disorders (PTLDs). Cytotoxic T lymphocytes directed against well-characterized epitopes of EBV latency genes represent an already successful and promising therapeutic approach to EBV-associated lymphomas, in particular PTLDs. Copyright 2001 S. Karger AG, Basel.

L16 ANSWER 5 OF 23 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2001:345077 BIOSIS
DOCUMENT NUMBER: PREV200100345077
TITLE: VEGF as a mediator of tumor-associated immunodeficiency.
AUTHOR(S): Ohm, Joyce E.; Carbone, David P. (1)
CORPORATE SOURCE: (1) Vanderbilt-Ingram Cancer Center, 648 Medical Research Building II, Nashville, TN, 37232: dcarbone@vanderbilt.edu USA
SOURCE: Immunologic Research, (2001) Vol. 23, No. 2-3, pp. 263-272. print.
ISSN: 0257-277X.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Decreased immune function in cancer patients is well-characterized (1), and tumor cells have developed a variety of mechanisms to avoid anti-tumor immune responses (2-8). One mechanism for inhibition of immune cell function by tumors is the production of soluble factors, such as IL-10, ***TNF*** , TGF-beta, and Vascular Endothelial Growth Factor (VEGF). The effects of these factors appear to be twofold: To inhibit effector function and to impair the development of immune cells by acting on earlier stages of immunopoiesis. Immune suppression by tumors is accomplished by a variety of cellular and molecular mechanisms, and

virtually all branches of the immune system can be affected. VEGF and its receptors have profound effects on the early development and differentiation of both vascular endothelial and hematopoetic progenitors (9). It induces proliferation of mature endothelial cells and is an important component in the formation of tumor neovasculature (10). VEGF is abundantly expressed by a large percentage of solid tumors and this over-expression is closely associated with a poor prognosis (11,12). Some of the earliest hematopoetic progenitors express receptors for VEGF (13), and we have demonstrated that VEGF causes a defect in the functional maturation of dendritic cells (DC) from progenitors. This developmental defect is associated with impaired ***activation*** of ***NF*** - ***kappaB*** (14-17). This ***review*** describes research demonstrating that VEGF is not only important for tumor vascularization, but is also a key factor produced by solid tumors to inhibit recognition and destruction of tumor cells by the immune system.

L16 ANSWER 6 OF 23 MEDLINE
ACCESSION NUMBER: 2001487959 IN-PROCESS
DOCUMENT NUMBER: 21421415 PubMed ID: 11529675
TITLE: Crosstalk between ***NF*** - ***kappaB***. - ***Activating*** and Apoptosis-Inducing Proteins of the ***TNF*** -Receptor Complex.
AUTHOR: Heyninck K; Beyaert R
CORPORATE SOURCE: Unit for Molecular Signal Transduction in Inflammation, Department of Molecular Biology, Flanders Interuniversity Institute for Biotechnology, University of Ghent, K. L. Ledeganckstraat 35, Ghent, B-9000, Belgium.
SOURCE: MOLECULAR CELL BIOLOGY RESEARCH COMMUNICATIONS, (2001 Sep) 4 (5) 259-65.
Journal code: DRR; 100889076. ISSN: 1522-4724.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20010903
Last Updated on STN: 20010903

AB The cytokine tumor necrosis factor (***TNF***) elicits a wide range of biological responses, including inflammation, cell proliferation, differentiation, and apoptosis. Although the molecular mechanisms of ***TNF*** signaling have been largely elucidated, the principle that regulates the balance of life and death is still unknown. This ***review*** will focus on the crosstalk that exists between proteins of the ***TNF*** receptor (***TNF*** -R) signalosome, and which are involved in the initiation of nuclear factor kappa B (***NF*** - ***kappaB***) ***activation*** or apoptosis. At least four different mechanisms of regulation can be distinguished: (i) ***NF*** - ***kappaB*** -mediated induction of proteins of the ***TNF*** -R complex; (ii) ***NF*** - ***kappaB*** -independent protection against apoptosis by the ***TNF*** -R-associating factor 2 (TRAF2)-mediated recruitment of antiapoptotic proteins; (iii) dual ***activation*** of apoptosis and ***NF*** - ***kappaB*** by a single molecule; and (iv) amplification of the death signal by proteolytic inactivation of signaling proteins that are involved in ***NF*** - ***kappaB*** ***activation*** or cell survival. Copyright 2001 Academic Press.

L16 ANSWER 7 OF 23 MEDLINE
ACCESSION NUMBER: 2001337848 MEDLINE
DOCUMENT NUMBER: 21109803 PubMed ID: 11167129
TITLE: Tumor necrosis factor receptor-associated factor (TRAF) 2

and its role in ***TNF*** signaling.

AUTHOR: Wajant H; Scheurich P

CORPORATE SOURCE: Institute of Cell Biology and Immunology, University of Stuttgart, Allmandring 31, Stuttgart 70569, Germany.. harald.wajant@po.uni-stuttgart.de

SOURCE: INTERNATIONAL JOURNAL OF BIOCHEMISTRY AND CELL BIOLOGY, (2001 Jan) 33 (1) 19-32. Ref: 104
Journal code: CDK; 9508482. ISSN: 1357-2725.

PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200106

ENTRY DATE: Entered STN: 20010618
Last Updated on STN: 20010618
Entered Medline: 20010614

AB Tumor necrosis factor (***TNF***) is the prototypic member of the ***TNF*** ligand family and has a key role in the regulation of inflammatory processes. ***TNF*** exerts its functions by interaction with the death domain-containing ***TNF*** -receptor 1 (***TNF*** -R1) and the non-death domain-containing ***TNF*** -receptor 2 (***TNF*** -R2), both members of a receptor family complementary to the ***TNF*** ligand family. Due to the prototypic features of the ***TNF*** receptors and their importance for the regulation of inflammation, the signal transduction mechanisms utilized by these receptors have been extensively studied. Several proteins that interact directly or indirectly with the cytoplasmic domains of ***TNF*** -R1 and ***TNF*** -R2 have been identified in the recent years giving ideas how these receptors are connected to the apoptotic pathway and the signaling cascades leading to ***activation*** of ***NF*** - ***kappaB*** and JNK. Of special interest are ***TNF*** receptor-associated factor (TRAF) 1 and 2, which defines a novel group of adaptor proteins involved in signal transduction by most members of the ***TNF*** receptor family, of IL-1 receptor and IL-17 receptor as well as some members of the TOLL-like receptor family. TRAF 2 is currently the best-characterized TRAF family member, having a key role in mediating ***TNF*** -R1-induced ***activation*** of ***NF*** - ***kappaB*** and JNK. Moreover, recent studies suggest that TRAF 2 represents an integration point for pro- and antiapoptotic signals. This ***review*** focuses on the molecular mechanisms that underlay signal initiation by ***TNF*** -R1 and ***TNF*** -R2, with particular consideration of the role of TRAF 2, and highlights the importance of this molecule for the integration of such antagonizing pathways as death induction and ***NF*** - ***kappaB*** -mediated surviving signals.

L16 ANSWER 8 OF 23 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:608927 CAPLUS

DOCUMENT NUMBER: 133:206904

TITLE: Human ***endokine*** alpha and methods of use

INVENTOR(S): Yu, Guo-Liang; Ni, Jian; Rosen, Craig A.

PATENT ASSIGNEE(S): Human Genome Sciences, Inc., USA

SOURCE: PCT Int. Appl., 263 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000050620	A2	20000831	WO 2000-US4722	20000225
WO 2000050620	A3	20001130		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 2000035017	A5	20000914	AU 2000-35017	20000225
PRIORITY APPLN. INFO.:			US 1999-122099 P	19990226
			US 1999-136788 P	19990528
			WO 2000-US4722 W	20000225

AB The present invention concerns a novel member of the tumor necrosis factor (TNF) family of cytokines. In particular, isolated nucleic acid mols. are provided encoding the ***endokine*** alpha protein. ***Endokine*** alpha polypeptides are also provided, as are vectors, host cells and recombinant methods for producing the same. Also provided are diagnostic and therapeutic methods concerning TNF family-related disorders.

L16 ANSWER 9 OF 23 MEDLINE
ACCESSION NUMBER: 2000495518 MEDLINE
DOCUMENT NUMBER: 20384621 PubMed ID: 10924851
TITLE: Recent advances towards understanding redox mechanisms in the ***activation*** of nuclear factor kappaB.
AUTHOR: Janssen-Heininger Y M; Poynter M E; Baeuerle P A
CORPORATE SOURCE: Department of Pathology, University of Vermont, Burlington, VT 05405, USA.. yjanssen@zoo.uvm.edu
CONTRACT NUMBER: RO1HL60014 (NHLBI)
SOURCE: FREE RADICAL BIOLOGY AND MEDICINE, (2000 May 1) 28 (9) 1317-27. Ref: 95
Journal code: FRE; 8709159. ISSN: 0891-5849.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20001027
Last Updated on STN: 20001027
Entered Medline: 20001019

AB The transcription factor, nuclear factor-kappaB (***NF*** - ***kappaB***) has been studied extensively due to its prominent role in the regulation of immune and inflammatory genes, apoptosis, and cell proliferation. It has been known for more that a decade that ***NF*** - ***kappaB*** is a redox-sensitive transcription factor. The contribution of redox regulation and the location of potential redox-sensitive sites within the ***NF*** - ***kappaB*** ***activation*** pathway are subject to intense debate due to many conflicting reports. Redox regulation of ***NF*** - ***kappaB*** has been extensively addressed in this journal and the reader is referred to two comprehensive reviews on the subject [1,2]. With the identification of signaling intermediates proximal to the degradation of the inhibitor, IkappaB, the number of

potential redox-sensitive sites is rapidly increasing. The purpose of this ***review*** is to address recent insights into the ***NF*** - ***kappaB*** signaling cascades that are triggered by proinflammatory cytokines such as ***TNF*** -alpha and IL-1beta. In addition, the role of nitrogen monoxide (.NO) in the regulation of ***NF*** - ***kappaB*** will be reviewed. Opportunities for redox regulation that occur upstream of IkappaB-alpha degradation, as well as the potential for redox control of phosphorylation of ***NF*** - ***kappaB*** subunits, will be discussed. Redox-sensitive steps are likely to depend on the nature of the ***NF*** - ***kappaB*** ***activator*** , the type of reactive oxygen or nitrogen species involved, the selectivity of signaling pathways ***activated*** , as well as the cell type under investigation. Lastly, it is discussed how redox regulation of ***NF*** - ***kappaB*** ***activation*** is likely to involve multiple subcellular compartments.

L16 ANSWER 10 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:34989 CAPLUS
DOCUMENT NUMBER: 135:120784
TITLE: NF-.kappa.B ***activation*** in inflammatory bowel disease
AUTHOR(S): Naito, Yuji; Takagi, Tomohisa; Yoshikawa, Toshikazu
CORPORATE SOURCE: First Department of Medicine, Kyoto Prefectural University of Medicine, Kyoto, 602-8566, Japan
SOURCE: Free Radicals Chem., Biol. Med. (2000), 501-513. Editor(s): Yoshikawa, Toshikazu. OICA International (UK) Ltd.: London, UK. CODEN: 69AUUF
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A ***review*** with 46 refs. Inflammatory bowel disease is a chronic inflammatory disease characterized by increased expression of inflammatory cytokines (IL-1.beta., ***TNF*** -.alpha., and IFN-.gamma.) and enzymes (inducible nitric oxide synthase and cyclooxygenase 2). Nuclear factor (NF)-.kappa.B is a transcription factor that regulates the ***activation*** of numerous genes in response to pathogens and proinflammatory cytokines, and is, therefore, pivotal in the initiation and perpetuation of chronic intestinal inflammation. The authors discuss here a series of recent studies that demonstrate NF-.kappa.B ***activation*** in the inflamed mucosa of animal models and patients with inflammatory bowel disease. There is increasing evidence that NF-.kappa.B is important in the pathophysiol. of inflammatory bowel disease; therefore, therapeutic interventions aimed at limiting NF-.kappa.B ***activation*** and down-regulating prodn. of inflammatory mediators could prove to be beneficial in decreasing host-derived tissue injury and colon dysfunction. These new insights into the regulation of NF-.kappa.B will benefit the future development of inflammatory bowel disease regimens with greater efficacy and less toxicity.
REFERENCE COUNT: 46
REFERENCE(S):
(1) Ardite, E; British Journal of Pharmacology 1998, V124, P431 CAPLUS
(3) Barnes, P; New England Journal of Medicine 1997, V336, P1066 CAPLUS
(4) Bertrand, V; European Cytokine Network 1998, V9, P161 CAPLUS
(5) Conner, E; Journal of Pharmacology and Experimental Therapeutics 1997, V282, P1615 CAPLUS
(6) Davidson, N; Journal of Experimental Medicine

09512363
1996, V184, P241 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 11 OF 23 MEDLINE
ACCESSION NUMBER: 2000206205 MEDLINE
DOCUMENT NUMBER: 20206205 PubMed ID: 10744338
TITLE: Inhibition of transcription factors by anti-inflammatory and anti-rheumatic drugs: can variability in response be overcome?.
AUTHOR: Handel M L; Nguyen L Q; Lehmann T P
CORPORATE SOURCE: University of New South Wales and Garvan Institute of Medical Research, Sydney, Australia.. mhandel@garvan.unsw.edu.au
SOURCE: CLINICAL AND EXPERIMENTAL PHARMACOLOGY AND PHYSIOLOGY, (2000 Mar) 27 (3) 139-44. Ref: 53
Journal code: DD8; 0425076. ISSN: 0305-1870.
PUB. COUNTRY: Australia
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000629
Last Updated on STN: 20000629
Entered Medline: 20000621

AB 1. The drugs used in the treatment of rheumatoid arthritis (RA) form a diverse group with unpredictable adverse effects, mostly weak efficacy and variable responses. Despite their differences, a common feature of many anti-inflammatory and disease-modifying anti-rheumatic drugs (DMARD) is inhibition of pro-inflammatory transcription factors, particularly nuclear factor (***NF***)- ***kappaB*** and ***activator*** protein (AP)-1. 2. The present brief ***review*** identifies those drugs capable of inhibiting transcription factors, particularly steroids, gold salts, D-penicillamine, cyclosporine A and possibly salicylates. 3. The newer biological inhibitors of tumour necrosis factor (***TNF***)-alpha and interleukin (IL)-1beta are capable of indirect inhibition of ***NF*** - ***kappaB*** ***activation*** , although even with these potent agents the problem of variability in response has not disappeared. 4. The development of selective inhibitors of the transcription factor ***NF*** - ***kappaB*** should have the benefit of the anti-inflammatory drugs and DMARD, both new and old. 5. It is hypothesized that this strategy will overcome much of the variability in the therapeutic response and adverse effects that limit the usefulness of the existing drugs in the treatment of RA.

L16 ANSWER 12 OF 23 MEDLINE
ACCESSION NUMBER: 2000071946 MEDLINE
DOCUMENT NUMBER: 20071946 PubMed ID: 10605930
TITLE: Oxidative stress and nuclear factor-kappaB ***activation*** : a reassessment of the evidence in the light of recent discoveries.
AUTHOR: Bowie A; O'Neill L A
CORPORATE SOURCE: Department of Biochemistry, Trinity College, Dublin, Ireland.. agbowie@tcd.ie
SOURCE: BIOCHEMICAL PHARMACOLOGY, (2000 Jan 1) 59 (1) 13-23. Ref: 97
Journal code: 9Z4; 0101032. ISSN: 0006-2952.
PUB. COUNTRY: ENGLAND: United Kingdom

09512363
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000114
Last Updated on STN: 20000114
Entered Medline: 20000106

AB Nuclear factor-kappaB (NFKB) is a transcription factor with a pivotal role in inducing genes involved in physiological processes as well as in the response to injury and infection. A model has been proposed whereby the diverse agents that ***activate*** NFkappaB do so by increasing oxidative stress within the cell. ***Activation*** of NFkappaB involves the phosphorylation and subsequent degradation of an inhibitory protein, IKB, and recently many of the proximal kinases and adaptor molecules involved in this process have been elucidated. Additionally, we now understand in detail the NFkappaB ***activation*** pathway from cell membrane to nucleus for interleukin-1 (IL-1) and tumour necrosis factor (***TNF***). This ***review*** revisits the evidence for the oxidative stress model in light of these recent findings, and finds little in the new information to rationalise or justify a central role for oxidative stress in ***NF*** - ***kappaB*** ***activation*** . We demonstrate that much of the evidence for the involvement of oxidative stress is either specific to a stimulus in a particular cell line or open to reinterpretation. In particular, the ***activation*** of NFkappaB by hydrogen peroxide is cell-specific and distinct from physiological ***activators*** such as IL-1 and ***TNF*** , while inhibition by antioxidants, also found to be cell- and stimulus-specific, can involve diverse and unexpected targets which may be distinct from redox modulation. We conclude that in most cases the role of oxidative stress in ***NF*** - ***kappaB*** ***activation*** is at best facilitatory rather than causal, if a role exists at all. In addition, other evidence suggests a role for lipid peroxides in pathways where such a role exists. In future, when a role for oxidative stress in a pathway is postulated, the challenge will be to show which particular kinases or adaptor molecules, if any, are redox-modulated.

L16 ANSWER 13 OF 23 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2000:149678 BIOSIS
DOCUMENT NUMBER: PREV200000149678
TITLE: Signal transduction in inflammatory processes, current and future therapeutic targets: A mini ***review*** .
AUTHOR(S): Witkamp, R.; Monshouwer, M. (1)
CORPORATE SOURCE: (1) Department of Metabolism and Pharmacokinetics, Pharmacia, and Upjohn, Viale Pasteur 10, 200014, Nerviano, MI Italy
SOURCE: Veterinary Quarterly., (Jan., 2000) Vol. 22, No. 1, pp. 11-16.
ISSN: 0165-2176.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The selective control of inflammatory reactions will continue to be a major reactions will continue to be a major issue in the development of new drugs. Many new molecular targets are coming up. This paper highlights a few key mediators that are nowadays considered as interesting therapeutic intervention points. Cytokines play an important regulatory role in the initiation, maintenance and termination of inflammatory

reactions. More than 50 cytokines have been identified, and more and more has become known about their receptors and signal transduction pathways. Tumour necrosis factor-alpha (***TNF*** -alpha) is still regarded as one of the initial cytokines of the cascade, and different approaches are followed to control its synthesis, release or effects. Lipopolysaccharide (LPS) is a one of the triggers that is able to induce a strong ***TNF*** -response. Inhibitors of cyclic nucleotide phosphodiesterases (PDEs), including rolipram and pentoxifylline suppress the LPS-induced ***TNF*** -alpha production in monocytes/ macrophages. In our laboratory it has been shown that the alternative way to increase cAMP levels, via stimulation of beta-adrenergic receptors, also provides an effective way, bot in vitro and in vivo, to inhibit ***TNF*** -alpha release. Other therapeutic ways include the use of antibodies directed to cytokines, ***TNF*** receptor fused to IgG, antibody therapy against ***TNF*** , the use of MAP kinase inhibitors. The different signal transduction pathways, including the ***NF*** - ***kappaB*** ***activation*** route may provide alternative pharmacological tools. We may surely expect anti-inflammatory drugs of much greater specificity to be developed in the next decade. Despite the relative limited investments in veterinary drug development this will also have consequences for veterinary therapy.

L16 ANSWER 14 OF 23 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 1
ACCESSION NUMBER: 2000:292169 BIOSIS
DOCUMENT NUMBER: PREV200000292169
TITLE: Polynucleotides encoding human ***endokine*** alpha.
AUTHOR(S): Yu, Guo-Liang (1); Ni, Jian; Rosen, Craig A.
CORPORATE SOURCE: (1) Laytonsville, MD USA
ASSIGNEE: Human Genome Sciences, Inc., Rockville, MD, USA; Human Genome Sciences, Inc.
PATENT INFORMATION: US 5998171 December 07, 1999
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Dec. 7, 1999) Vol. 1229, No. 1, pp. No pagination. e-file..
ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
AB The present invention novel member of the tumor necrosis factor (TNF) family of cytokines. In particular, isolated nucleic acid molecules are provided encoding the ***endokine*** alpha protein. ***Endokine*** alpha polypeptides are also provided, as are vectors, host cells and recombinant methods for producing the same. Also provided are diagnostic and therapeutic methods concerning TNF family-related disorders.

L16 ANSWER 15 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:436244 CAPLUS
DOCUMENT NUMBER: 131:335413
TITLE: Nuclear factor .kappa.B (NF-.kappa.B) pathway as a therapeutic target in rheumatoid arthritis
AUTHOR(S): Jue, Dae-Myung; Jeon, Kye-Im; Jeong, Jae-Yeon
CORPORATE SOURCE: Department of Biochemistry, College of Medicine, The Catholic University of Korea, Seoul, 137-701, S. Korea
SOURCE: J. Korean Med. Sci. (1999), 14(3), 231-238
CODEN: JKMSEH; ISSN: 1011-8934
PUBLISHER: Korean Academy of Medical Science
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A ***review*** with 79 refs. Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by persistent joint swelling and progressive destruction of cartilage and bone. Current RA treatments are

largely empirical in origin and their precise mechanism of action is uncertain. Increasing evidence shows that chronic inflammatory diseases such as RA are caused by prolonged prodn. of proinflammatory cytokines including tumor necrosis factor (***TNF***) and interleukin 1 (IL-1). The nuclear factor .kappa.B (NF-.kappa.B) plays an essential role in transcriptional ***activation*** of ***TNF*** and IL-1. NF-.kappa.B is induced by many stimuli including ***TNF*** and IL-1, forming a pos. regulatory cycle that may amplify and maintain RA disease process. NF-.kappa.B and enzymes involved in its ***activation*** can be a target for anti-inflammatory treatment. Aspirin and sodium salicylate inhibit ***activation*** of NF-.kappa.B by blocking I.kappa.B kinase, a key enzyme in NF-.kappa.B ***activation*** . Glucocorticoids suppress expression of inflammatory genes by binding glucocorticoid receptor with NF-.kappa.B, and increasing expression of inhibitory protein of NF-.kappa.B, I.kappa.B.alpha.. Sulfasalazine and gold compds. also inhibit NF-.kappa.B ***activation*** .

REFERENCE COUNT: 79

REFERENCE(S):
(2) Auphan, N; Science 1995, V270, P286 CAPLUS
(3) Barnes, P; N Engl J Med 1997, V336, P1066 CAPLUS
(4) Beg, A; Science 1996, V274, P782 CAPLUS
(5) Bondeson, J; Biochem Pharmacol 1995, V50, P1753 CAPLUS
(6) Bouma, M; J Immunol 1994, V153, P4159 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 16 OF 23 MEDLINE DUPLICATE 2

ACCESSION NUMBER: 2000054362 MEDLINE
DOCUMENT NUMBER: 20054362 PubMed ID: 10585776

TITLE: Characterization of TNFRSF19, a novel member of the tumor necrosis factor receptor superfamily.

AUTHOR: Hu S; Tamada K; Ni J; Vincenz C; Chen L
CORPORATE SOURCE: Mayo Graduate and Medical Schools, Mayo Clinic, Rochester, Minnesota 55905, USA.

SOURCE: GENOMICS, (1999 Nov 15) 62 (1) 103-7.
Journal code: GEN; 8800135. ISSN: 0888-7543.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF173166
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000218
Last Updated on STN: 20000218
Entered Medline: 20000204

AB By searching the expressed sequence tag database, a novel murine tumor necrosis factor receptor designated TNFRSF19 was identified. TNFRSF19 cDNA encodes a putative membrane protein of 348 amino acids with one incomplete and two complete cysteine-rich motifs within its extracellular region and a large cytoplasmic domain. TNFRSF19 mRNA can be detected in most murine tissues examined, particularly in brain, reproductive organs, and late developmental stages of murine embryo, but not in tissues of the immune system. The cell surface expression of the ligand of TNFRSF19 is highly restricted. Of 22 human and murine cell lines examined by FACS analysis, only Raji (B cell lymphoma cell line), GM847 (fibroblast cell line), 293 (embryonic kidney cell line), and K562 (chronic myeloid leukemia) were positive. TNFRSF19 did not bind newly cloned TNF ligands, including TWEAK (HGMW-approved symbol TNFSF12), VEGI/TL1 (HGMW-approved symbol TNFSF15), TL6/ ***endokine*** (HGMW-approved symbol TNFSF18), APRIL (HGMW-approved symbol TNFSF13), OPGL (HGMW-approved symbol TNFSF11), LIGHT

(HGMW-approved symbol TNFSF14), or BAFF/THANK (HGMW-approved symbol TNFSF13B) by enzyme-linked immunosorbent assay and FACS analyses. Overexpression of TNFRSF19 transduced neither apoptotic signaling nor signals leading to NF-kappaB induction. Taken together with the data that the TNFRSF19 extracellular domain-immunoglobulin fusion protein did not affect the allogeneic mixed lymphocyte reaction, our data indicate that TNFRSF19 is not involved in the modulation of immune responses. Copyright 1999 Academic Press.

L16 ANSWER 17 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:121402 CAPLUS
DOCUMENT NUMBER: 130:350805
TITLE: ***Activation*** of Nf-.kappa.B by inflammatory cytokines
AUTHOR(S): Rothe, M.
CORPORATE SOURCE: Tularik, Inc., Two Corporate Drive, South San Francisco, CA, 94080, USA
SOURCE: Symp. Immunol. VIII: Inflammation, 8th (1999), Meeting Date 1998, 31-42. Editor(s): Eibl, Martha M. Springer: Berlin, Germany.
CODEN: 67HZAV
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A ***review*** and discussion with many refs. Tumor necrosis factor, plays a central role in generation of inflammatory responses. ***TNF*** ***activates*** the transcription of many genes encoding acute phase and proinflammatory proteins which bring about changes that characterize the inflammatory phenotype. This function is mediated primarily by the transcription factor nuclear factor .kappa.B. The activities of the recently reported IKKs [I.kappa.B-.alpha. and IKK-1 (CHUK) and IKK-.beta. (Ikk-2)], novel serine-threonine kinases, represent catalytic subunits of a large I.kappa.B kinase complex that links the ***TNF*** - and IL-1-induced kinase cascades to NF-.kappa.B ***activation*** . The interactions of these components are described.
REFERENCE COUNT: 86
REFERENCE(S): (1) Baeuerle, P; Annu Rev Immunol 1994, V12, P141 CAPLUS
(2) Baeuerle, P; Cell 1996, V87, P13 CAPLUS
(3) Baldwin, A; Annu Rev Immunol 1996, V14, P649 CAPLUS
(4) Barnes, P; N Engl J Med 1997, V336, P1066 CAPLUS
(5) Boldin, M; J Biol Chem 1995, V270, P7795 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 18 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:151264 CAPLUS
DOCUMENT NUMBER: 128:201816
TITLE: Cloning of human ***endokine*** .alpha. cDNA and its diagnostic and therapeutic uses
INVENTOR(S): Yu, Guo-Liang; Ni, Jian; Rosen, Craig A.
PATENT ASSIGNEE(S): Human Genome Sciences, Inc., USA; Yu, Guo-Liang; Ni, Jian; Rosen, Craig A.
SOURCE: PCT Int. Appl., 79 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9807880	A1	19980226	WO 1996-US13282	19960816
W: AM, AU, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IL, JP, KG, KP, KR, KZ, LT, LV, MD, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, UA, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9668478	A1	19980306	AU 1996-68478	19960816
AU 731123	B2	20010322		
EP 961831	A1	19991208	EP 1996-928886	19960816
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2000516474	T2	20001212	JP 1998-510675	19960816

PRIORITY APPLN. INFO.: WO 1996-US13282 W 19960816

AB The present invention concerns a novel member of the tumor necrosis factor (TNF) family of cytokines. In particular, isolated nucleic acid mols. are provided encoding the ***endokine*** .alpha. protein. ***Endokine*** .alpha. polypeptides are also provided, as are vectors, host cells and recombinant methods for producing the same. Human ***endokine*** .alpha. cDNA was isolated and sequenced from a human brain striatum cDNA library, and expressed sequence tags corresponding to a portion of the ***endokine*** .alpha. cDNA were also found in several endothelial libraries and a fetal liver library. ***Endokine*** .alpha. cDNA comprises and open reading frame encoding a polypeptide of 169 amino acid residues including an N-terminal methionine, an intracellular domain of 17 amino acid residues, a transmembrane domain of 26 amino acids, an extracellular domain of 126 amino acids, and a deduced mol. wt. of about 19 kDa. Epitope-conferring regions are also defined. Also provided are diagnostic and therapeutic methods concerning TNF family-related disorders.

L16 ANSWER 19 OF 23 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1999:79326 CAPLUS

DOCUMENT NUMBER: 130:236094

TITLE: TRAIL induces apoptosis and ***activation*** of NF.kappa.B

AUTHOR(S): Jeremias, Irmela; Debatin, Klaus Michael

CORPORATE SOURCE: Deutsches Krebsforschungszentrum, Heidelberg, 60120, Germany

SOURCE: Eur. Cytokine Network (1998), 9(4), 687-688
CODEN: ECYNEJ; ISSN: 1148-5493

PUBLISHER: John Libbey Eurotext

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A ***review*** with 14 refs. TRAIL (***TNF*** -related-apoptosis-inducing-ligand) was found as a new member of the ***TNF*** family which mediates cell death in a wide variety of malignant cell lines and primary tumor cells. TRAIL induces two different signals, cell death mediated by caspases and gene induction mediated by NF.kappa.B. Inhibition of TRAIL-induced ***activation*** of NF.kappa.B augments apoptosis induction by TRAIL and attenuates apoptosis resistance.

REFERENCE COUNT: 14

REFERENCE(S): (1) Beg, A; Science 1996, V274, P782 CAPLUS
(2) Das, K; J Biol Chem 1997, V272, P14914 CAPLUS
(3) Degli-Esposti, M; Immunity 1997, V7, P813 CAPLUS
(4) Gura, T; Science 1997, V277, P768 CAPLUS
(5) Irmler, M; Nature 1997, V388, P190 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 20 OF 23 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1998:343971 BIOSIS
DOCUMENT NUMBER: PREV199800343971
TITLE: Apoptosis signaling by death receptors.
AUTHOR(S): Schulze-Osthoff, Klaus (1); Ferrari, Davide; Los, Marek; Wesselborg, Sebastian; Peter, Marcus E.
CORPORATE SOURCE: (1) Dep. Internal Med. I, Med. Clin., Eberhard-Karls-Univ., Otfried-Mueller-Str. 10, D-72076 Tuebingen Germany
SOURCE: European Journal of Biochemistry, (June, 1998) Vol. 254, No. 3, pp. 439-459.
ISSN: 0014-2956.
DOCUMENT TYPE: General Review
LANGUAGE: English
AB Death receptors have been recently identified as a subgroup of the ***TNF*** -receptor superfamily with a predominant function in induction of apoptosis. The receptors are characterized by an intracellular region, called the death domain, which is required for the transmission of the cytotoxic signal. Currently, five different such death receptors are known including tumor necrosis factor (***TNF***) receptor-1, CD95 (Fas/APO-1), ***TNF*** -receptor-related apoptosis-mediated protein (TRAMP) and ***TNF*** -related apoptosis-inducing ligand (TRAIL) receptor-1 and -2. The signaling pathways by which these receptors induce apoptosis are rather similar. Ligand binding induces receptor oligomerization, followed by the recruitment of an adaptor protein to the death domain through homophilic interaction. The adaptor protein then binds a proximal caspase, thereby connecting receptor signaling to the apoptotic effector machinery. In addition, further pathways have been linked to death receptor-mediated apoptosis, such as sphingomyelinases, JNK kinases and oxidative stress. These pro-apoptotic signals are counteracted by several mechanisms which inhibit apoptosis at different levels. This ***review*** summarizes the current and rapidly expanding knowledge about the biological functions of death receptors and the mechanisms to trigger or to counteract cell death.

L16 ANSWER 21 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:559421 CAPLUS
DOCUMENT NUMBER: 129:301297
TITLE: Redox regulation of the nuclear factor kappa B (NF-.kappa.B) signaling pathway and disease control
AUTHOR(S): Okamoto, Takashi; Sakurada, Shinsaku; Yang, Jian-Ping; Takahashi, Naoko
CORPORATE SOURCE: Dep. Mol. Genet., Nagoya City Univ. Med. Sch., Mizuho-cho, Mizuho-ku, Nagoya, 467, Japan
SOURCE: Keio Univ. Symp. Life Sci. Med. (1998), 1(Oxygen Homeostasis and Its Dynamics), 438-449
CODEN: KUSMF9
PUBLISHER: Springer-Verlag Tokyo
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A ***review*** with 74 refs. Nuclear factor kappa B (NF-.kappa.B) is an inducible cellular transcription factor that ***activates*** various cellular and viral genes. NF-.kappa.B usually exists as a mol. complex with an inhibitory mol., I.kappa.B, in the cytosol. On stimulation of the cells, such as by proinflammatory cytokines IL-1 and tumor necrosis factor (***TNF***), I.kappa.B is dissocd. and NF-.kappa.B is translocated to the nucleus and ***activates*** the expression of the target genes. The authors found that a redox control mechanism is involved in the DNA-binding activity of NF-.kappa.B and that a cellular-reducing catalyst thioredoxin (Trx), together with kinases, is

primarily involved as an effector mol. in this signaling pathway. Trx was recently demonstrated to assoc. with the redox-sensitive cysteine within the DNA-binding loop of NF-.kappa.B. Effects of antioxidants in blocking NF-.kappa.B ***activation*** can be explained by the involvement of radical oxygen intermediates (ROI) in this pathway. These findings support the idea that redox regulation involving ROI and Trx plays a crucial role in the signal transduction pathway leading to NF-.kappa.B ***activation*** , thus contributing substantially to understanding of pathogenic processes of various diseases including AIDS, hematogenic cancer cell metastasis, and rheumatoid arthritis (RA).

L16 ANSWER 22 OF 23 MEDLINE
ACCESSION NUMBER: 1998400136 MEDLINE
DOCUMENT NUMBER: 98400136 PubMed ID: 9730685
TITLE: HIV-1 tat molecular diversity and induction of ***TNF*** -alpha: implications for HIV-induced neurological disease.
AUTHOR: Mayne M; Bratanich A C; Chen P; Rana F; Nath A; Power C
CORPORATE SOURCE: Department of Medical Microbiology, University of Manitoba, Winnipeg, Canada.
SOURCE: NEUROIMMUNOMODULATION, (1998 May-Aug) 5 (3-4) 184-92. Journal code: CCL; 9422763. ISSN: 1021-7401.
PUB. COUNTRY: Switzerland
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 19990106
Last Updated on STN: 19990106
Entered Medline: 19981103

AB ***Activation*** and infection by HIV-1 of glial cells and infiltrating macrophages are cardinal features of AIDS-related neurological disease. Tumor necrosis factor-alpha (***TNF*** -alpha) is released by these cell types, and increased ***TNF*** -alpha mRNA and protein levels are associated with the development and severity of HIV-induced neurological disease. HIV-1 proteins have been implicated in HIV neuropathogenesis including Tat which has been shown to be a potent inducer of ***TNF*** -alpha. We ***review*** our data showing the induction of ***TNF*** -alpha by Tat in primary human fetal astrocytes, human peripheral blood mononuclear cells, macrophages, and astrocytic and macrophage cell lines. ***TNF*** -alpha induction was ***NF*** -***kappaB*** dependent and was eliminated by inhibiting protein kinase A, phospholipase C and protein tyrosine kinase activity. In addition, we examined the molecular diversity of the tat genome in the brains of HIV-infected patients from different HIV-1 clades. Comparison of matched brain- and spleen-derived tat sequences indicated that homology among brain-derived clones was greater than that between the brain- and spleen-derived clones. The brain-derived tat sequences were markedly heterogeneous in regions which influence viral replication and intracellular transport. Future studies using Tat, encoded by different sequences, will be necessary to determine the functional significance of tat molecular diversity. Nonetheless, these studies suggest that Tat is an important inducer of ***TNF*** -alpha production and thus may play a key role in the pathogenesis of HIV-related neurological disease.

L16 ANSWER 23 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:757395 CAPLUS
DOCUMENT NUMBER: 128:19092
TITLE: Multiple redox regulation in NF-.kappa.B transcription factor ***activation***

L16 ANSWER 1 OF 23 MEDLINE
ACCESSION NUMBER: 2001456063 IN-PROCESS
DOCUMENT NUMBER: 21392983 PubMed ID: 11502073
TITLE: Mediators of inflammation and acute phase response in the liver.
AUTHOR: Streetz K L; Wustefeld T; Klein C; Manns M P; Trautwein C
CORPORATE SOURCE: Dept. of Gastroenterology and Hepatology, Medizinische Hochschule Hannover, Germany.
SOURCE: CELLULAR AND MOLECULAR BIOLOGY, (2001 Jun) 47 (4) 661-73. Journal code: BNA; 9216789. ISSN: 0145-5680.
PUB. COUNTRY: France
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20010815
Last Updated on STN: 20010815

AB The acute phase response is a generalized response of the organism to multiple disturbances of its physiological homeostasis. It consists of local and systemic reactions. Inflammatory processes are the main causes for the initiation of these defence mechanisms. Responsible mediators for the acute phase response are predominantly cytokines, whereby the liver is the predominant target organ. Changes in hepatocyte gene expression profiles result in dramatic changes in serum concentrations of specific plasma proteins, called acute phase proteins. IL-6 was identified as the principal mediator of this reaction. Via its cellular signal transducer gp130 IL-6 induces DNA-binding of STAT transcription factors on regulatory elements of target genes. While IL-6 dependent processes are mainly conferred to be protective other inflammatory cytokines are attributed to be cytotoxic for the liver. ***TNF*** -alpha was shown to be involved in several models of liver failure as a mediator for both cytotoxicity and cell proliferation. ***TNF*** -alpha leads via caspases to the onset of apoptosis, the so-called programmed cell death. On the other hand it ***activates*** ***NF*** - ***kappaB*** thereby triggering inflammatory processes. In this ***review*** we display the relevance for intracellular actions of both cytokines in several models of liver injury. Especially we refer to the T-cell mediated Concanavalin A induced liver failure and to liver regeneration induced by CCL4 and partial hepatectomy. Both cytokines contribute in concert to a cellular balance during these pathophysiological conditions.

L16 ANSWER 2 OF 23 MEDLINE
ACCESSION NUMBER: 2001311627 MEDLINE
DOCUMENT NUMBER: 21278352 PubMed ID: 11384837
TITLE: The ***TNF*** -receptor-associated factor family: scaffold molecules for cytokine receptors, kinases and their regulators.
AUTHOR: Wajant H; Henkler F; Scheurich P
CORPORATE SOURCE: Institute of Cell Biology and Immunology, University of Stuttgart, Allmandring 31, 70569, Stuttgart, Germany.. harld.wajant@po.uni-stuttgart.de
SOURCE: CELLULAR SIGNALLING, (2001 Jun) 13 (6) 389-400. Ref: 159 Journal code: AVB; 8904683. ISSN: 0898-6568.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107

09512363

AUTHOR(S): Piette, Jacques; Piret, Bernard; Bonizzi, Guiseppina; Schoonbroodt, Sonia; Merville, Marie Paule; Legrand-Poels, Sylvie; Bours, Vincent

CORPORATE SOURCE: Lab. Virology, Inst. Pathology, Univ. Liege, Liege, B-4000, Belg.

SOURCE: Biol. Chem. (1997), 378(11), 1237-1245
CODEN: BICHF3; ISSN: 1431-6730

PUBLISHER: Walter de Gruyter & Co.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A ***review*** is given with many refs. The well-known Rel/NF-.kappa.B family of vertebrate transcription factors comprises a no. of structurally related, interacting proteins that bind DNA as dimers and whose activity is regulated by subcellular location. This family includes many members (i.e. p50, p52, RelA, RelB, c-Rel), most of which can form DNA-binding homo- or heterodimers. All Rel proteins contain a highly conserved domain of approx. 300 amino-acids, called the Rel homol. domain (RH), which contains sequences necessary for the formation of dimers, nuclear localization, DNA binding, and I .kappa.B binding. Nuclear expression and consequent biol. action of the eukaryotic NF-.kappa.B transcription factor complex are tightly regulated through its cytoplasmic retention by ankyrin-rich inhibitory proteins known as I.kappa.B. The I.kappa.B proteins include a group of related proteins that interact with Rel dimers and regulate their activities. The interaction of a given I.kappa.B protein with a Rel complex can affect the Rel complex in distinct ways. In the best characterized example, I.kappa.B-.alpha. interacts with a p50/RelA (NF-.kappa.B) heterodimer to retain the complex in the cytoplasm and inhibit its DNA-binding activity. The NF-.kappa.B/I.kappa.B-.alpha. complex is located in the cytoplasm of most resting cells, but can be rapidly induced to enter the cell nucleus. Upon receiving a variety of signals, many of which are probably mediated by the generation of reactive O species (ROS), I.kappa.B-.alpha. undergoes phosphorylation at Ser residues by a ubiquitin-dependent protein kinase, is then ubiquitinated at nearby Lys residues and finally degraded by the proteasome, probably while still complexed with NF-.kappa.B. Removal of I.kappa.B-.alpha. uncovers the nuclear localization signals on subunits of NF-.kappa.B, allowing the complex to enter the nucleus, bind to DNA and affect gene expression. Like pro-inflammatory cytokines (e.g. IL-1, ***TNF***), various ROS (i.g. peroxides, singlet O) as well as UV (C to A) light are capable of mediating NF-.kappa.B nuclear translocation, while the sensor mols. which are sensitive to these agents and trigger I.kappa.B-.alpha. proteolysis are still unidentified. A ROS-independent mechanism is ***activated*** by IL-1.beta. in epithelial cells and seems to involve the acidic sphingomyelinase/ceramide transduction pathway.

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(FILE 'HOME' ENTERED AT 19:13:28 ON 18 OCT 2001)

FILE 'MEDLINE, EMBASE, BIOSIS, CAPLUS' ENTERED AT 19:13:37 ON 18 OCT 2001

L1 10499 S NF-KAPPAB
L2 316202 S CYTOKINE OR TNF OR ENDOKINE
L3 3630 S L1 AND L2
L4 8 S ENDOKINE
L5 2 S L4 AND L1
L6 1 DUP REM L5 (1 DUPLICATE REMOVED)

L7	141838	S	TNF
L8	2579	S	L7 AND L1
L9	2435309	S	ACTIVAT?
L10	2258	S	L9 AND L8
L11	2794473	S	REVIEW
L12	27	S	L10 AND L11
L13	19	DUP REM	L12 (8 DUPLICATES REMOVED)
L14	0	S	L13 AND L4
L15	27	S	L13 OR L4
L16	23	DUP REM	L15 (4 DUPLICATES REMOVED)